SUMMARY OF DATA FOR CHEMICAL SELECTION

Potassium Ferricyanide

13746-66-2

BASIS OF NOMINATION TO THE CSWG

Potassium ferricyanide is brought to the attention of the CSWG as a widely used chemical with significant human exposure potential, positive mutagenicity data, and no PEL or TLV.

More than eighty thousand workers are potentially exposed to potassium ferricyanide. Exposure of the general population to potassium ferricyanide occurs primarily through its use in photographic processing, particularly in home and school darkrooms. Very little information on the toxicity of
potassium ferricyanide was found in the available literature. In a recent study, potassium ferricyanide induced DNA synthesis and cell replication in serum starved PC12 cells. The chronic effects of potassium ferricyanide are not well characterized.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee (ITC), Environmental Protection Agency (EPA), provided information on the annual production range of potassium ferricyanide.

SELECTION STATUS

ACTION BY CSWG: 6/22/99

Studies requested:

- Standard battery of genotoxicity tests including Ames *Salmonella* and micronucleus assays
- 90-day toxicity testing

Priority:

Moderate

Rationale/Remarks:

- Widespread exposure of workers and consumers from its use in photographic darkrooms
- Suspicion of toxicity based on redox potential, not on presence of cyanide moiety
- Lack of data to characterize toxicity of compound
- NCI will conduct mouse lymphoma and Ames *Salmonella* assays

CHEMICAL IDENTIFICATION

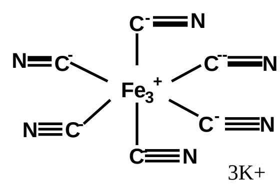
CAS Registry Number: 13746-66-2

Chemical Abstracts Service Name: Ferrate (3-), hexakis (cyano-C)-, tripotassium (OC-6-11) (9CI)

Synonyms: Iron potassium cyanide; Potassium ferricyanide; Prussian Red; Red prussiate; Tripotassium hexa-cyanoferrate

Structural Class: Metal complexed nitrile

Structure, Molecular Formula and Molecular Weight:



$K_3Fe(CN)_6$ Mol. wt.: 329.25

Chemical and Physical Properties:

Description: Ruby-red crystals or powder (Budavari, 1996; Lewis, 1993)

Solubility: Slowly soluble in 2.5 parts cold water, in 1.3 parts boiling water; slightly soluble in alcohol (Budavari, 1996)

Stability: Stable under normal temperatures and pressures; decomposes on strong heating to evolve highly toxic fumes (Lewis, 1993; Fisher Scientific, 1998)

Reactivity: Releases hydrogen cyanide gas if heated, if hot acid is added, or if exposed to strong ultraviolet light (McCann, 1994)

Technical Products and Impurities: Potassium ferricyanide is available in research quantities at a purity of >99% from Aldrich Chemical Co., Inc. and Sigma Chemical Co. (Aldrich Chemical Co., Inc., 1998; Sigma Chemical Co., 1998).

EXPOSURE INFORMATION

Production and Producers: Potassium ferricyanide is derived by passing chlorine into a solution of potassium ferrocyanide; potassium ferricyanide separates out (Lewis, 1993).

Potassium ferricyanide is listed in the EPA's Toxic Substances Control Act (TSCA) Inventory (NLM, 1999). US production of potassium ferricyanide in 1993 was reported to be between 10,000 and 1 million lbs based on non-confidential data received by the EPA (Walker, 1998). No other quantitative information was found in the available literature.

According to recent issues of chemical directories, potassium ferricyanide is manufactured and/or distributed by Allchem Industries, Inc., AC Industries, Inc., Allan Chemical Corp., Charkit Chemical Corp., Dastech International, Inc., Fabrichem, Inc., The Graymor Chemical Corp., RIA International, Mays Chemical Co., Seachem, Spectrum Quality Products, Inc., U.P.T Chemical, Inc., Wego Chemical & Mineral Corp., Westco Chemical, Inc., F.H. Taussig, Inc., United Mineral & Chemical Corp., Noah Technologies Corp., Alfa Aesar, GFS Chemicals, Inc. (Chemical Information Services, 1994; Hunter, 1997; Kuney, 1997; McCoy, 1997).

The Port Import/Export Reporting Service (PIERS) reported potassium ferricyanide imports of 819,057 pounds over the 13 month period from January 1998 to February 1999 (Dialog Information Service, 1999). The US International Trade Administration reported potassium ferricyanide imports for consumption of 730,756 pounds for the year 1998, an increase from the reported imports for consumption of 387,493 pounds in 1997 (ITA, 1999).

Use Pattern: Potassium ferricyanide is widely used as a chemical reducer in photographic processing to remove silver from negatives and positives (dot etching). This is done to compensate for minor errors in a photograph or to make deliberate changes in the reproduction. In color reproduction of photographs, potassium ferricyanide is used to reduce the size of dots on halftone positives without reducing their density and, thereby, reducing the amount of color in treated areas. This is the most important means of manual color correction of original color photographs. Potassium ferricyanide can be purchased both as ready-to-use brand name products (*i.e.*, Farmer's reducer), or as the individual chemical, which can be mixed by an individual. In black and white processing, film developing is usually done in closed canisters. Print processing uses tray processing, with successive developing baths, stop baths, fixing baths, and rinse steps. Color processing is more complicated than black and white processing, and there is a wide variation in processes used by different companies. Color processing can be done in trays or in automatic processors (Bruno, 1982; McCann, 1994).

Potassium ferricyanide is also used in tempering iron and steel, sensitive coatings on blueprint paper, wood staining, dyeing wool, production of pigments, electroplating, as a laboratory reagent, and a mild oxidizing agent in organic synthesis (Budavari, 1996; Lewis, 1993).

Currently, there are 1744 patents on file with the US Patents and Trademark Office that use potassium ferricyanide in some capacity (US Patents and Trademark Office, 1999).

Human Exposure: The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 85,385 workers, including 20,227 female workers, were potentially exposed to potassium ferricyanide in the workplace. The NOES database does not contain information on the frequency, level or duration of exposure to workers of any chemicals listed therein (NLM, 1999).

There is potential for widespread low-level exposure to potassium ferricyanide in the general population from its use in photographic processing, sensitive coatings on blueprint paper, and as a laboratory reagent.

Chemistry labs and art departments in high schools, colleges, and universities across the country stock the chemical. A report from Lycoming College's Art Department stated that "because of the toxicity of the chemicals used to process color film, students are encouraged to wear masks. When developing black and white film, masks and gloves are available, but not required" (Lycoming College, 1999).

Potassium ferricyanide is sold on the internet as part of a "Photographic Chemistry Kit" for junior and senior high school chemistry, photography and physics classes. It is advertised that 15 pairs of students can complete a series of experiments illustrating light activated chemical reactions (Midcoast, 1999).

Environmental Occurrence: No information on the natural or environmental occurrence of potassium ferricyanide was identified in the available literature.

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace allowable levels of potassium ferricyanide. Potassium ferricyanide was not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a threshold limit value (TLV) or biological exposure index (BEI) are made.

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: Potassium ferricyanide will release hydrogen cyanide gas if heated, if hot acid is added, or if exposed to strong ultraviolet light. Cases of cyanide poisoning have occurred through treating Farmer's reducer with acid (McCann, 1994).

A 38-year-old woman attempted suicide by ingesting one coffee spoon of potassium ferricyanide and alcohol. The amount of potassium ferricyanide in the blood could not be measured directly. However, mild methemoglobinemia was observed and subsided spontaneously within eight hours after ingestion. Chest and abdomen x-rays failed to reveal any abnormality. Blood cyanide concentrations in the patient remained well below the toxic levels in humans. Repeated measurements of arterial blood gases, anion gap and lactate levels remained within normal range. The clinical course was uneventful and the patient was extubated 12 h after admission. The authors suspected that only a small amount of potassium ferricyanide was absorbed and that the toxicity due to the ingestion of a single dose of potassium ferricyanide in humans is minimal. As very little cyanide seems to be released from the complex, specific antidotal therapy to cyanide is therefore not required (Hantson *et al*., 1996).

No epidemiological studies or case reports investigating the association of exposure to potassium ferricyanide and cancer risk in humans were identified in the available literature.

Animal Data: Gavage LD_{50} values of 2,970 mg/kg and 3,439 mg/kg in mice and 4,520 mg/kg and 5,300 mg/kg in rats were reported for potassium ferricyanide (Besedina *et al.*, 1986a; Talakin *et al.*, 1986).

No 2-year carcinogenicity studies of potassium ferricyanide in animals were identified in the available literature.

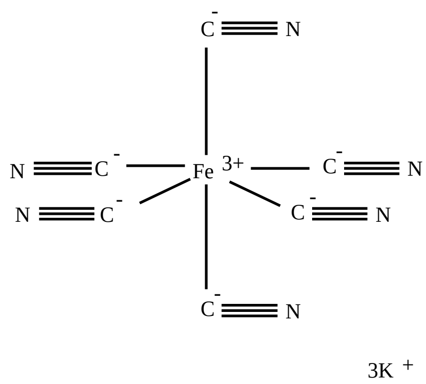
A study of the general toxicity of potassium ferricyanide from 6-months of exposure and potential allergenicity from epicutaneous and inhalation intake, reproductive function in female rats, and gonadotoxic effects formed the basis for establishing a mean 24-hour atmospheric air maximum allowable concentration (MAC) of 0.04 mg/m^3 (Besedina et al., 1986b).

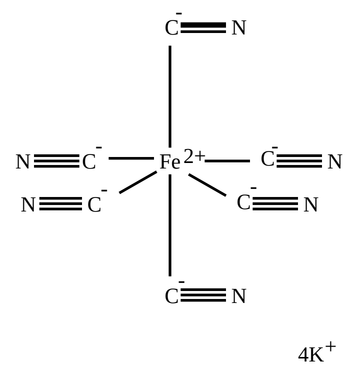
Short-TermTests: Potassium ferricyanide at concentrations of 1-3000 nM/plate had no mutagenic activity in *Salmonella typhimurium* strain TA102 (Marzin & Hung, 1985). Potassium ferricyanide (100 mM) induced weak gene conversions and reverse mutations in the D7 strain of *Saccharomyces cerevisiae* (Singh, 1983). Nishioka (1975) reported that potassium ferricyanide was negative in *B. subtilis* rec assay in strains H17 and M45. Ellem and Kay (1983) reported that potassium ferricyanide at concentrations of 0.003-0.1 mM stimulated the growth of human melanoma cells (MM96 wild type) when serum reduction was a limiting growth factor. Potassium ferricyanide (100 mM) induced DNA synthesis and cell replication in serum starved PC12 cells (Thomas *et al*., 1996).

Metabolism: Inhalation of 2000 mg/m^3 of potassium ferricyanide by rats and mice led to accumulations of ferricyanide in the blood and urine by the first day. Almost total excretion of potassium ferricyanide took place via urine by the first day after administration (STN, 1999a).

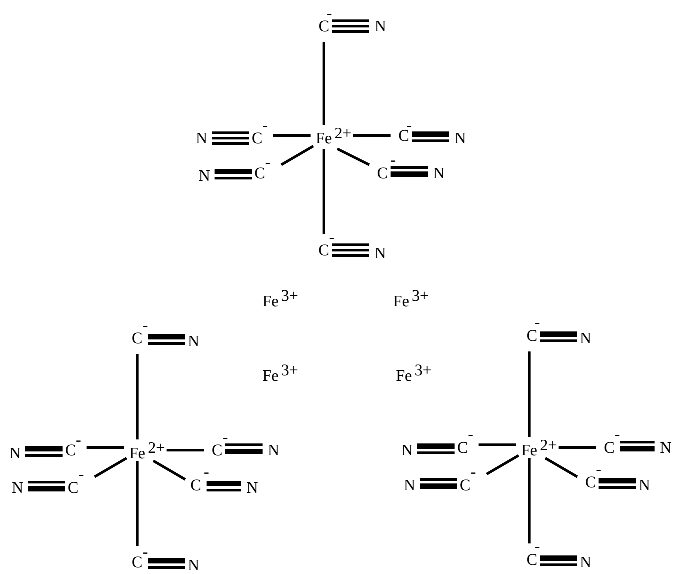
Hantson and coworkers (1996) reported that no reliable data concerning the bioavailability of potassium ferricyanide seems to exist while the bioavailability of cyanide from hexacyanoferrate, which was investigated in humans, was very poor.

Structure-Activity Relationships: Two chemicals structurally similar to potassium ferricyanide were screened for relevant information associating these chemicals with a mutagenic or carcinogenic effect. Structures of potassium ferricyanide and these structurally similar compounds are shown below.





Potassium ferricyanide **Potassium ferrocyanide**



Prussian Blue

Mutagenicity data were available for one of the compounds. Potassium ferrocyanide [13943-58-3] was negative in *B. subtilis* rec assay strains H17 and M45 (Nishioka, 1975). No data on carcinogenicity or mutagenicity were found for Prussian blue [14038-43-8]. The role of the different valence states for iron could not be determined from the limited data available in the literature on all three compounds.

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